

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Photofrin 75 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 75 mg of porfimer sodium.

After reconstitution, the final concentration of porfimer sodium solution is 2.5 mg/mL (see section 6.6)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Solution for Injection.

A dark red to reddish brown lyophilised powder (or cake) for reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Photodynamic therapy (PDT) with Photofrin is indicated for:

- palliative treatment of obstructing endobronchial nonsmall cell lung cancer;
- palliative treatment of obstructing oesophageal cancer.

4.2 Posology and method of administration

Photodynamic therapy (PDT) with Photofrin is a two-stage process requiring administration of both medicinal product and light. Physicians should be trained in the use of photodynamic therapy. The first stage of PDT is the intravenous injection of Photofrin at a dose of 2 mg/kg. The second stage of therapy is illumination with laser light 40-50 hours following injection with Photofrin. Patients may receive a second laser light application 96-120 hours after medicinal product administration. Therefore, one course of PDT consists of one injection plus one or two light applications. Up to 2 more courses of medicinal product and light may be given, with each injection separated by a minimum of 30 days.

Photofrin Administration

Photofrin should be reconstituted according to the directions given in section 6.6, and administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. As with all intravenous injections, care should be taken to prevent extravasation at the injection site. If extravasation does occur, the area should be protected from light for at least 30 days and up to 90 days or more. There is no known benefit from injecting the extravasation site with another substance.

Photoactivation of Photofrin

Photofrin is activated by light in the spectral region of 630 nm. Approximately 40-50 hours after Photofrin administration, laser light should be delivered to the tumour by a cylindrical fibre optic diffuser or a microlens fibre optic passed through the operating channel of an endoscope/bronchoscope.

Light Doses: Photoactivation of Photofrin is controlled by the total light energy (light dose) delivered to the tumour site and depends on the indication and the means of light delivery, as follows:

- For endobronchial tumours, the cylindrical diffuser will be suitable for most tumours. The light dose for endobronchial tumours using the cylindrical diffuser is 200 joules/cm of tumour

length. Alternatively, the microlens fibre optic may be appropriate for small, flat, non-circumferential tumours. The light dose using the microlens fibre optic is 100 joules/cm².

- For oesophageal tumours, a light dose of 300 joules/cm of tumour length should be delivered using a cylindrical diffuser.

Cylindrical Diffuser (Endobronchial or Oesophageal Lesions): The cylindrical diffuser uniformly distributes laser light radially in a cylindrical pattern over the entire length of the fibre optic tip. The following light dosimetry equation applies.

$$\text{Light dose (J/cm)} = \frac{\text{Total power output from diffuser (W) x Treatment time (seconds)}}{\text{Diffuser length (cm)}}$$

For example, the total power output from the diffuser, as measured by a suitable integrating sphere power meter, could be set to [400 mW/cm x length of diffuser in cm] which will deliver the appropriate dose using exposure times of either 8 minutes, 20 seconds (endobronchial tumours, 200 J/cm) or 12 minutes, 30 seconds (oesophageal tumours, 300 J/cm).

Cylindrical diffusers are available in several lengths and the diffuser tip length should be chosen to match the length of the tumour. Tumours with lengths that differ from available diffuser lengths may require multiple use of a single diffuser or the use of two or more diffusers of differing lengths. Diffuser length should be sized to avoid exposure of non-malignant tissue to light and to prevent overlapping of previously treated malignant tissue. Diffusers or combinations of diffusers should be selected to minimise patient treatment time.

The cylindrical diffusers may be used either interstitially or intraluminally. For non-circumferential endobronchial tumours that are soft enough to penetrate, interstitial fibre placement is preferred to intraluminal activation, since this method produces better efficacy and results in less exposure of normal bronchial mucosa to the light. When the interstitial technique is used, up to 90% of the length of the diffuser should be inserted into the tumour mass.

Microlens (Endobronchial lesions only): The microlens fibre optic delivers a diverging, forward-directed beam of light similar to that produced by a torch. It is used to treat small lesions by positioning the microlens tip so that the lesion is uniformly illuminated by a circular spot. The diameter of the spot can be increased or decreased by moving the microlens tip further from or nearer to the lesion. The following light dosimetry equation applies:

$$\text{Light dose (J/cm}^2\text{)} = \frac{\text{Total power output at fibre tip (W) x Treatment time (seconds)}}{\text{Treatment area (cm}^2\text{)}}$$

For example, the power output at the microlens fibre tip, as measured by a power meter, could be set to [200 mW/cm² x tumour area in cm²]. This will deliver the dose of 100 J/cm² of tumour using an exposure time of 8 minutes, 20 seconds per area treated.

Debridement and Retreatment

In patients with endobronchial tumours, debridement is mandatory to remove necrotic tumour debris and clear secretions or mucous plugs, thereby preventing possible dyspnoea, obstruction, atelectasis and infection. For oesophageal cancer, debridement is optional since the residua will be removed naturally by peristaltic action. Debridement of residua should be performed 2 days after light treatment. Patients with residual tumour may be retreated with laser light at the time of debridement at the same dose as used for the initial treatment. The second light dose should be administered 96 to 120 hours after the Photofrin injection.

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each injection separated by a minimum of 30 days) can be given. Before each course of treatment, patients should be evaluated for the presence of a tracheo-oesophageal or

broncho-oesophageal fistula or for the possibility that the tumour may be eroding into a major blood vessel (see section 4.3).

Use in Children and Adolescents

Safety and effectiveness in children and adolescents have not been established. Photofrin should not be used in children or adolescents until further data are available.

Use in Elderly Patients

Approximately 70% of the patients treated with PDT using Photofrin in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

Use in Patients with Impaired Hepatic or Renal Function

The influence of impaired hepatic function on Photofrin disposition has not been evaluated.

4.3 Contraindications

- Hypersensitivity to porphyrins or to any of the excipients.
- Porphyria.
- Severe hepatic and/or renal impairment.
- Tracheo-oesophageal or broncho-oesophageal fistula.
- Suspected erosion of major blood vessels due to risk of massive, potentially fatal haemorrhage.
- For emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection with Photofrin and laser light treatment.

4.4 Special warnings and precautions for use

Photodynamic therapy with Photofrin should be used only in clinics or centres with experience of endoscopic laser procedures.

All patients who receive Photofrin will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for at least 30 days. Patients with mild to moderate hepatic impairment should be clearly informed that the period requiring the precautionary measures described above may be longer than 90 days. The photosensitivity is due to residual medicinal product which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is, however, beneficial because the remaining medicinal product will be inactivated gradually and safely through a photobleaching reaction.

Therefore, patients should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, oedema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. Some patients may remain photosensitive for up to 90 days or more. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. **Conventional ultraviolet (UV) sunscreens will only protect against UV light- related photosensitivity and will be of no value in protecting against Photofrin-induced photosensitivity reactions caused by visible light.**

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received porfimer sodium. For at least 30 days and up to 90 days, when outdoors, patients should wear dark sunglasses, which have an average white light transmittance of <

4%. Patients should be advised to consult their ophthalmologist if they notice any vision changes after treatment with Photofrin and PDT.

PDT has not been studied in patients with significant cardio-pulmonary symptoms. The effect on such patients is not known.

The mechanism of action of PDT in tumor's microvasculature leads to vascular stasis and thrombosis lesions which may increase a risk of thrombo-embolic events especially in patients with history of cardiovascular diseases and/or after major surgical procedures.

As the result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

The inflammatory response from PDT will depend on the tumour size and extent of surrounding normal tissue that receives light. It is recommended that two to four weeks be allowed after PDT before commencing radiotherapy. Similarly, if PDT is to be given after radiotherapy, at least four weeks should be allowed to pass between the two treatments in order for the acute inflammatory reaction from radiotherapy to subside.

The risk of acute hypersensitivity reaction including anaphylaxis cannot be ruled out (see section 4.8). In case of allergic reaction, treatment should be stopped immediately and appropriate emergency measures initiated.

Oesophageal Cancer

If the oesophageal tumour is eroding into the trachea or bronchial tree, the likelihood of tracheo-oesophageal or broncho-oesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

Patients with oesophageal varices should be treated with extreme caution. Light should not be given directly to the variceal area because of the high risk of bleeding.

Lung Cancer

Patients should be assessed for tumours that may be eroding into a pulmonary blood vessel. Patients at high risk for fatal massive haemoptysis include those with large, centrally located tumours, those with cavitating tumours or those with extensive tumour extrinsic to the bronchus.

If the endobronchial tumour invades deeply into the bronchial wall, the possibility exists for fistula formation upon resolution of tumour.

PDT should be used with extreme caution for endobronchial tumours in locations where treatment-induced inflammation could obstruct the main airway, e.g., long or circumferential tumours of the trachea, tumours of the main carina that involve both mainstem bronchi circumferentially, or circumferential tumours in the remaining mainstem bronchus of patients with prior pneumonectomy.

Patients with endobronchial lesions must be closely monitored between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress (see section 4.2).

Inflammation and mucositis may result from exposure of normal tissue to too much light.

Necrotic debris may also obstruct the airway. If respiratory distress occurs, the physician should be prepared to carry out immediate bronchoscopy to remove secretions and debris to open the airway.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies of Photofrin and any other medicinal products. However, it is possible that concomitant use of other photosensitising agents (e.g., tetracyclines, sulphonamides, phenothiazines, sulphonylurea hypoglycaemic agents, thiazide diuretics, and griseofulvin) could increase the photosensitivity reaction.

Photofrin PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischaemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many medicinal products could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulphoxide, β -carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischaemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with Photofrin PDT. Medicinal products that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

4.6 Fertility, pregnancy and lactation

There are no adequate clinical data on exposed pregnancies available for porfimer sodium. Animal studies showed no teratogenicity although some foetotoxic effects were observed (see section 5.3). Photofrin should not be used during pregnancy unless clearly necessary. It is not known whether porfimer sodium is excreted into human breast milk. Women receiving Photofrin should not breast feed.

Women of childbearing potential should practice an effective method of contraception during and for at least 90 days after the PDT period and have a pre- treatment pregnancy test performed.

4.7 Effects on ability to drive and use machines

Photofrin has no or negligible influence on ability to drive and use machines. For the PDT procedure, sedation may be required consequently caution should be taken. Patients should not drive or use machines after light treatment if they have been sedated for the procedure.

4.8 Undesirable effects

Systemically induced effects associated with PDT with Photofrin consist of photosensitivity and mild constipation. All patients who receive Photofrin will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see section 4.4). Photosensitivity reactions consist mainly of mild erythema on the face and hands. Photosensitivity reactions are avoidable through proper patient education.

Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect. Rashes have been observed in association with photodynamic therapy. Case reports of fluid imbalance have been reported.

Endobronchial Cancer

Very common ($>10/100$) and common ($>5/100$ to $<10/100$) adverse events reported in patients ($n=99$) with obstructing endobronchial cancers treated with porfimer sodium with PDT are listed below.

Fatal massive haemoptysis, with or without prior radiotherapy, has been observed with greater frequency in the PDT-treated group. In half of the patients with fatal haemoptysis, the event occurred more than 30 days after the last treatment procedure and was judged by the investigator to be unrelated to PDT. Fatal massive haemoptysis may be due to disease progression or due to resolution of tumour eroding into a major blood vessel (see section 4.3). Inflammatory reactions manifested as fever,

bronchitis and chest pain. Cough, dyspnoea, haemoptysis and increased sputum, while reported as adverse events, are also symptoms of the disease.

Serious and other notable adverse events observed in clinical trials in less than 5% of PDT-treated patients with endobronchial cancer included: lung abscess, pleural effusion, pulmonary embolism and pulmonary thrombosis.

Table 1. Summary of Adverse Events in Endobronchial Cancer Patients

<u>Psychiatric disorders</u> <i>Common:</i> Anxiety, Insomnia
<u>Respiratory, thoracic and mediastinal disorders</u> <i>Very Common:</i> Haemoptysis, Pneumonia, Bronchitis, Dyspnoea, Cough
<u>Gastrointestinal disorders</u> <i>Common:</i> Constipation, Dyspepsia
<u>Skin and subcutaneous tissue disorders</u> <i>Very Common:</i> Photosensitivity reaction
<u>Musculoskeletal, connective tissue and bone disorders</u> <i>Common:</i> Back pain
<u>General disorders and administration site conditions</u> <i>Very Common:</i> Pyrexia

Oesophageal Cancer

Very common (>10/100) and common (>5/100 to <10/100) adverse events reported in patients (n=127) who had completely or partially obstructing oesophageal cancer treated with porfimer sodium PDT are presented below.

Serious and other notable adverse events observed in less than 5% of patients included: abnormal vision, angina pectoris, bradycardia, bronchitis, bronchospasm, diplopia, eye pain, gastric ulcer, ileus, jaundice, laryngotracheal oedema, myocardial infarction, oesophageal perforation, oesophagitis, peritonitis, photophobia, pneumonitis, pulmonary haemorrhage, pulmonary oedema, respiratory failure, sick sinus syndrome, stridor, supraventricular tachycardia.

Table 2. Summary of Adverse Events in Oesophageal Cancer Patients

<u>Infections and infestations</u> <i>Common:</i> Sepsis, Urinary tract infection, Candidiasis
<u>Blood and lymphatic system disorders</u> <i>Very Common:</i> Anaemia
<u>Metabolism and nutrition disorders</u> <i>Common:</i> Dehydration, Anorexia
<u>Psychiatric disorders</u> <i>Very Common:</i> Insomnia <i>Common:</i> Confusional state

<u>Cardiac disorders</u> <i>Common:</i> Cardiac failure, Atrial fibrillation, Tachycardia
<u>Vascular disorders</u> <i>Common:</i> Hypertension, Hypotension
<u>Respiratory, thoracic and mediastinal disorders</u> <i>Very Common:</i> Respiratory distress, Pleural effusion, Pneumonia, Dyspnoea, Pharyngitis <i>Common:</i> Tracheo-oesophageal fistula
<u>Gastrointestinal disorders</u> <i>Very Common:</i> Abdominal pain (upper, lower), Constipation, Vomiting, Nausea <i>Common:</i> Oesophageal stenosis, Haematemesis, Oesophagebleeding, Oesophageal oedema, Dysphagia, Diarrhoea, Dyspepsia
<u>Skin and subcutaneous tissue disorders</u> <i>Very Common:</i> Photosensitivity reaction
<u>Musculoskeletal and connective tissue disorders</u> <i>Common:</i> Back pain
<u>General disorders and administration site conditions</u> <i>Very Common:</i> Chest pain, Pyrexia, Pain <i>Common:</i> Generalized oedema, Oedema peripheral, Asthenia
<u>Investigations</u> <i>Common:</i> Weight decreased

These effects were generally mild or moderate in severity and easily managed. Anaemia was not due to myelosuppression, but rather it was due to tumour bleeding and was more common in patients with large tumours (>10 cm) and with tumours in the lower third of the oesophagus. Tumour bleeding may be exacerbated by vigorous debridement. Debridement is optional in patients with oesophageal cancer (see section 4.2). The syndrome of respiratory insufficiency included one patient who experienced upper airway oedema (1%) and one who experienced bronchospasm during debridement (1%); the remaining events (8%) did not appear to be related to PDT. Fever and pleural effusion, as well as pain, oesophageal oedema and atrial fibrillation are thought to be manifestations of a local/regional inflammatory reaction. Oesophageal oedema occurred more frequently when the tumour was located in the upper third of the oesophagus; atrial fibrillation was more likely to occur when the tumour was in the middle third of the oesophagus.

Photosensitivity reactions occurred in approximately 20% of patients treated with Photofrin in clinical studies. Typically these reactions were mostly mild to moderate erythema but they also included swelling, itching, burning sensation, feeling hot or blisters.

In a single study of 24 healthy subjects, some evidence of photosensitivity reactions occurred in all subjects. Other less common skin manifestations were also reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin decolouration, skin nodules, increased wrinkles, increased skin fragility. These manifestations may be attributable to a pseudoporphyria state (temporary medicinal product-induced cutaneous porphyria).

Post Marketing Experience

The following adverse reactions, presented by system organ class in alphabetical order, have been identified during post-approval use of PDT with porfimer sodium and may depend on the treated areas and the underlying diseases. Because these reactions are reported voluntarily from a population of uncertain size, the frequency is not known (cannot be estimated from the available data). Please note that some reactions are related to PDT procedure or PDT device.

Blood and lymphatic system disorders: Anaemia, Leukocytosis

Cardiac disorders: Atrial fibrillation, Atrioventricular blocks first degree, Bradycardia

Eye disorders: Asthenopia, Cataract, Ocular hyperaemia

Gastrointestinal disorders: Dysphagia, Gastric ulcer, Gastrointestinal necrosis, Haematemesis, Dry lips, Nausea, Oedema mouth, Odynophagia, Oesophageal fistula, Oesophageal pain, Oesophageal perforation, Oesophageal stenosis, Oesophageal ulcer, Oesophagitis, Oral pain, Pancreatitis, Tracheo-oesophageal fistula, Vomiting

General disorders and administration site conditions: Application site oedema, Asthenic conditions (Asthenia, Fatigue and Malaise), Chest pain/discomfort, Chills, Oedema peripheral, Pyrexia, Swelling

Hepatobiliary disorders: Portal vein thrombosis

Immune system disorders: Hypersensitivity

Injury, poisoning and procedural complications: Bronchial injury, Oesophageal injury

Investigations: Activated partial thromboplastin time prolonged, C-reactive protein increased, Erythropenia, Haemoglobin decreased, Protein total decreased, Prothrombin time prolonged, Blood urea increased, Visual acuity test abnormal

Metabolism and nutrition disorders: Dehydration, Fluid overload, Hypocalcaemia

Nervous system disorders: Dizziness, Hypoaesthesia, Syncope vasovagal

Renal and urinary disorders: Bladder spasm, Dysuria, Hydronephrosis, Micturition urgency, Nocturia, Urinary retention

Respiratory, thoracic and mediastinal disorders: Bronchial fistula, Bronchial haemorrhage, Cough, Dyspnoea, Haemoptysis, Hiccups, Pleural effusion, Pulmonary embolism

Skin and subcutaneous tissue disorders: Angioedema, Blister, Dry skin, Erythema, Face oedema, Generalized erythema, Photodermatitis, Photosensitivity reaction, Pigmentation disorder, Pruritus, Pseudoporphyria, Rash, Rash generalized, Skin burning sensation, Sunburn, Urticaria

Vascular disorders: Deep vein thrombosis, Embolism, Hypotension, Phlebitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

Overdose of Photofrin

There is no information on overdose situations involving Photofrin. Higher than recommended medicinal product doses of two 2 mg/kg doses given two days apart (10 patients) and three 2 mg/kg doses given within two weeks (1 patient) were tolerated without notable adverse reactions. Effects of overdose on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of Photofrin is administered. In the event of an overdose, patients should protect their eyes

and skin from direct sunlight or bright indoor lights for 30 to 90 days. At this time, patients should test for residual photosensitivity (see section 4.4). Photofrin is not dialysable.

Overdose of Laser Light Following Photofrin

There is no information on overdose of laser light following porfimer sodium injection in patients with oesophageal carcinoma.

Endobronchial Cancer

Light doses of two to three times the recommended dose have been administered to a few patients with superficial endobronchial tumours. One patient experienced life-threatening dyspnoea and the others had no notable complications. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic Agents, ATC Code: L01X D01: Sensitizers used in photodynamic/radiation therapy

The cytotoxic and antitumour actions of Photofrin are light and oxygen-dependent. Photodynamic therapy (PDT) with Photofrin is a 2-stage process. The first stage is the intravenous injection of Photofrin. Clearance from a variety of tissues occurs over 40-72 hours, but tumours, skin, and organs of the reticuloendothelial system (including liver and spleen) retain Photofrin for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumour and dysplastic tissue selectivity in treatment may occur partly through selective retention of Photofrin but mainly through a selective delivery of light. Cellular damage caused by Photofrin PDT is a consequence of the propagation of free radical reactions. Radical initiation may occur after Photofrin absorbs light to form a porphyrin excited state. Spin transfer from Photofrin to molecular oxygen may then generate singlet oxygen.

Subsequent free radical reactions can form superoxide and hydroxyl radicals. Tumour death also occurs through ischaemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A₂ release. The laser treatment induces a photochemical, not a thermal, effect. The necrotic reaction and associated inflammatory response evolve over several days.

5.2 Pharmacokinetic properties

General Characteristics

A pharmacokinetic study was conducted in 12 endobronchial cancer patients given 2 mg/kg of Photofrin intravenously. Samples of plasma were obtained out to 56 days (1,344 hours) post injection and total porphyrin units determined. The mean peak plasma concentration (C_{max}) immediately following injection was 79.6 µg/mL (C.V. 61%, range 39-222); the mean T_{1/2} was 515 hours, i.e. 21.5 days (C.V. 26%, range 264-672). Thus, porfimer sodium is cleared slowly from the body, with a mean CL_T of 0.859 mL/h/kg (C.V. 53%).

The pharmacokinetics of Photofrin was also studied in 24 healthy subjects who received a single dose of 2 mg/kg Photofrin given via the intravenous route. Blood samples were obtained and pharmacokinetic parameters were calculated for 23 subjects (11 men and 12 women). Serum samples were collected out to 36 days after injection. The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The elimination half-life was 415 hours (17 days). C_{max} was determined to be 40 µg/mL, and AUC(inf) was 2400 µg/h/mL.

In vitro binding of Photofrin to human serum protein is around 90% and independent of concentration between 20 and 100 µg/mL. Preclinical studies indicate that the excretion of Photofrin components occurs primarily via the faecal route.

Characteristics in Specific Populations

The influence of renal and hepatic impairment on exposure to Photofrin has not been evaluated.

Gender had no effect on pharmacokinetic parameters except for t_{max} , which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of Photofrin in men and women were very similar.

Pharmacokinetics of Photofrin has not been established in children and adolescents.

5.3 Preclinical safety data

Photofrin was not mutagenic in standard genotoxicity tests in the absence of light. With light activation, Photofrin was mutagenic in some in-vitro tests. Foetotoxicity, but not teratogenicity, occurred in rats and rabbits only at elevated intravenous doses (greater than or equal to 4 mg/kg) and at greater dose frequency (daily) compared to the clinical dose regimen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Sodium hydroxide (may be added to adjust pH).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder: 8 years

After Reconstitution: use immediately (within 3 hours)

Chemical and physical in-use stability has been demonstrated for 24 hours at 3°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store below 25°C

In order to protect from light, keep the vial in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

75 mg powder in a vial (glass type I, 40 mL capacity) with a grey butyl stopper Pack size: 1 vial.

6.6 Special precautions for disposal <and other handling>

Photofrin 75 should be reconstituted with 31.8 mL of 5% glucose intravenous infusion resulting in a final concentration of 2.5 mg/mL. Do not use other diluents. Do not mix Photofrin with other medicinal products in the same solution. Sufficient vials of Photofrin should be reconstituted to provide the patient with a dose of 2 mg/kg using the calculation below. For most patients (up to 75 kg) two vials of Photofrin 75 will suffice.

$$\text{Photofrin (mL)} = \frac{\text{Patient's weight (kg)} \times 2 \text{ mg/kg}}{2.5 \text{ mg/mL}} = 0.8 \times \text{Patient's weight}$$

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-02-20